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Population pharmacokinetic-pharmacodynamic modelling of liquid and controlled-release formulations of oxycodone in healthy subjects

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Running title: Pharmacokinetic-pharmacodynamic modelling of different oxycodone formulations

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Abstract

Oral controlled-release formulations are playing an ever-increasing role in opioid therapy; however, little is known about their influence on the relationship between pharmacokinetics and pharmacodynamics.

The study aim was to characterise the pharmacokinetic-pharmacodynamics of two controlled-release tablet formulations and a liquid formulation of oxycodone in healthy, opioid-naïve subjects, which can serve as a reference for future patient studies.

A semi-double-blinded, three-way cross-over study was conducted, with fifteen healthy subjects receiving two differently designed 20 mg monophasic controlled-release oxycodone tablets and 10 mg oral solution oxycodone in a randomised order. Venous plasma concentrations and pupil diameter were determined pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 5, 6, 8, 12 and 24 h post-dose.

Oxycodone pharmacokinetics were best described by a two-compartment model with first order absorption. The controlled-release formulations had an absorption lag of 0.23 h and a slower absorption rate constant (k_{aCR} = 0.19 h^{-1}) compared to the oral solution (k_{aSOL} = 0.94 h^{-1}). Effects on pupil diameter were delayed relative to plasma (14 min half-life) for all formulations and were best described by a proportional E_{max} model. The plasma concentration of oxycodone at half-maximum effect was lower in males (31.1 μg/L) compared to females (52.8 μg/L; P <0.001).

The absorption profile of controlled-release oxycodone formulations provided a prolonged onset and offset of action compared to oral solution oxycodone. The controlled-release formulations showed no differences in pharmacokinetic and pharmacodynamic parameters suggesting that both may be used interchangeably in humans with normal gastrointestinal function.

Introduction

Pain is a complex pathology causing aggravation, depression, labour incapability and a deprived quality of life for many patients. Consequently, it can be a huge financial burden for societies worldwide [1]. Pain management is complex and opioids are often used in the treatment of chronic moderate to severe pain [2]. Oral controlled-release formulations are playing an ever-increasing role in drug therapy mainly due to their advantages of increasing dosing intervals and decreasing fluctuations in plasma concentrations, which improves patient compliance, efficacy and reduces occurrence of side-effects such as sedation [3–5]. However, drug release, and hence absorption,

from controlled-release formulations is highly dependent on formulation design, physiochemical drug properties and gastrointestinal physiology, where factors such as gastrointestinal fluid composition, motility, pH, transit time, surface area and/or distribution of metabolising enzymes and transporters play a crucial role [6]. Several controlled-release delivery systems exist. Some consist of hydrophilic polymers, which swell and form a gel network upon contact with gastrointestinal fluids, hereby controlling drug release. Others rely on lipases and bile salts to digest the hydrophobic matrix, thus gradually releasing the active ingredient [6]. Establishing a pharmacokinetic-pharmacodynamic (PKPD) model for different controlled-release formulations of oxycodone in healthy subjects is the first step towards investigating clinically relevant PKPD alterations in various patient groups, as this will serve as a reference to help explain variations and optimise treatment regimens. Pupillometry has previously been acknowledged as a reliable and objective surrogate for the pharmacodynamic effects of opioids, as it reflects the central opioid receptor activity [7–10]. A negative correlation has also been found between the extent of pupil constriction and analgesic effect after morphine exposure [11]. Furthermore, the onset of analgesia occurred simultaneously with the induced miosis [11]. We hypothesised that the pharmacodynamic (PD) time-course of controlled-release formulations would be explained entirely by the pharmacokinetic (PK) time-course, and that this would differ from the PK time-course of the oral solution in healthy subjects. The aim of this study was to characterise and evaluate the PKPD relationship of oxycodone following two generically marketed but differing controlled-release formulations and an oral solution in healthy subjects, using pupil diameter as a PD endpoint.

Materials and methods

Study design

This study was conducted in accordance with the Declaration of Helsinki, local regulations, the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [12] and International Conference on Harmonisation Good Clinical Practice (GCP) guidelines. The protocol, amendments and informed consent form were approved by The North Denmark Region Committee on Health Research Ethics, Denmark (N-20170039), the Danish Health and Medicines Authority (EudraCT No.: 2017-000732-34), the Data Protection Agency (ID. No. 2017-125), Denmark and registered in clinicaltrialsregister.eu (2017-000732-34). The study was monitored by

the GCP unit, Aalborg and Aarhus University Hospitals, Denmark. All participants gave their informed consent and received remuneration for their contribution.

The study was conducted according to a randomised, semi-blinded, three-way crossover design with at least 1-week washout interval. Researchers and nurses were blinded until all subjects had completed the study. The laboratory technician determining the plasma concentrations of oxycodone was fully blinded. The healthy subjects were unaware of dose and functionality of the different formulations; however, the drug formulations did not have identical appearances, hence being "semi-blinded". The study was conducted in a laboratory at Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital in the period of August 2017 to February 2018. Each subject fasted 8 h prior to study days and was supplied with standardised meals every 3 h post-dose until discharge. Water was allowed *ad libitum* except for 1 h before and after drug administration. Additionally, cordial or juice was allowed *ad libitum* at 3 h post-dose. Subjects were discharged after the 12 h blood sample and returned the subsequent morning for the 24 h blood sample. The study was conducted in a quiet laboratory setting under dimmed light conditions and tests were performed by trained investigators. Subjects were requested to restrict medications (apart from contraception), supplements, alcohol and products containing grapefruit 48 h prior to and during study days. Study data were collected and managed using REDCap electronic data capture tools hosted at Aalborg University Hospital [13].

Study population

An approximately even distribution of fifteen healthy, opioid-naïve men and women of Northern European descent, aged 25-80 years with a BMI between 18.5-29.9 kg/m^2 were recruited. An objective examination of the subjects was performed by a medical doctor. Subjects were judged healthy if they had no concurrent or past medical history of any chronic diseases, had normal vital signs and normal or non-clinically significant eGRF, ALAT, bilirubin, haemoglobin and HbA1c levels. Fertile females were required to have a negative pregnancy test and use an effective contraception method during the entire study period. Subjects were excluded if they had: Any known allergies to oxycodone or similar compounds, persistent pain, participated in other intervention studies within 14 days prior to study inclusion, expected need for new medication or surgery within the time course of the study, daily alcohol and/or nicotine consumption, daily intake of any medication and/or herbal medicines that could influence the study results (e.g. strong

inhibitors or inducers of CYP enzymes and P-glycoprotein), were lactating and/or had a personal or family history of substance abuse.

Study medication

On study days each subject received a single 10 mg oral solution oxycodone (Oxynorm®, oral liquid mixture 1mg/ml; Norpharma A/S / Mundipharma A/S, Vedbaek, Denmark) or 20 mg controlled-release (water-swellable matrix) oxycodone (Oxycodone hydrochlorid "Lannacher", controlled-release tablet 20 mg; Lannacher Heilmittel Ges.m.b.H, Lannach, Austria) or 20 mg controlled-release (lipid-based matrix) oxycodone (Oxycodone Depot "Sandoz", controlled-release tablet 20 mg; Sandoz A/S, Copenhagen, Denmark) in a randomised order. Subjects received the oral solution with 50 ml water and the tablets with 240 ml water. Each of the three drug formulations used was from the same batch.

Blood sampling

Venous blood samples were collected into K_2-EDTA vacutainers for quantification of oxycodone plasma concentrations before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 5, 6, 8, 12 and 24 h after drug administration. Blood samples were immediately cooled and subsequently centrifuged at 4°C at 2500 revolutions per minute for 15 minutes. Plasma was separated into duplicate polypropylene tubes and then stored at -80°C until analysis. The time between sample collection and freezer storage did not exceed 2 h.

Pupillometry

Pupillometry was used as an objective surrogate for the central nervous system (CNS) actions of oxycodone. Pupillary recordings were performed using a digital infrared hand-held NeuroOptics VIP 200 pupillometer (NeuroOptics, Irvine, CA, USA). A tight-fitting eyecup covered the eye during pupillary recordings. Recordings were conducted on the right eye, in a room with controlled dimmed lighting after each blood sampling. If subjects left the room or used an electronic device, a minimum of two minutes of dark adaption was mandatory before performing the pupillometry recording. Subjects were asked to look at the same fixation point with the left eye for each measurement. The pupil diameter was calculated as a mean of three successive recordings, which had a standard deviation below 0.1 mm.

Plasma analysis of oxycodone

Plasma samples were analysed for contents of oxycodone and noroxycodone on a Bruker Avance UHPLC (Bruker Daltonik, Bremen, Germany) equipped with a CTC-PAL-xt autosampler with cooled sample compartments (10 °C) and a column oven held at 40°C. The UHPLC eluate was directed to a Bruker Evoq Elite triple quadrupole MS equipped with a heated electrospray ionisation source. Separation was obtained using a Phenomenex (Phenomenex, Torrance, CA, USA) Kinetex XB-C_{18} column (50 mm × 2.1 mm i.d., 1.7 µm particle size) equipped with a guard column. Protein was removed from the plasma samples through protein crash by ice-cold acetonitrile; 600 µl acetonitrile and 10 µl internal standard (containing 300 ng/ml oxycodone-d_3 and 100 ng/ml noroxycodone-d_3; both from Cerrilliant Corporation, Round Rock, TX, USA) were added to an Eppendorf tube followed by the addition 200 µL plasma. The samples were vortexed for 10 seconds before centrifugation at 16,000 × *g* for 10 minutes. The supernatant was transferred to a deep well plate and evaporated to dryness in an RVC 2-25 CDPlus rotational vacuum concentrator (Christ, Osterode am Harz, Germany) set at 25°C. The residue was reconstituted in 100 µL mobile phase A. The reconstituted samples were analysed for contents of oxycodone and noroxycodone by injecting 15 µL on the above-mentioned UHPLC-TQMS system. The analytes were separated using a solvent system consisting of 15 mM ammonium formate in Milli-Q water (pH 3.5) (mobile phase A) and 15 mM ammonium formate in 90% acetonitrile (mobile phase B). HPLC grade acetonitrile was purchased from VWR – Bie & Berntsen (Søborg, Denmark), water was prepared by deionization and 0.22 µm membrane filtration using a Milipore system (Billerica, MA, USA), and ammonium formate was purchased from Sigma-Aldrich (St. Louis, MO, USA). The initial mobile phase composition of 3.5% B was changed to 75% B over 2 minutes after injecting the samples. The solvent composition was increased to 100% B at 2.1 min and kept at 100% B until 3 min., before returning to 3.5 %B (3.1 min) for column equilibration for additional 2.9 min. For the entire 6-minute cycle, the flow rate was kept at 500 µL/min. The mass spectrometer was operated in positive mode with multiple reaction monitoring. The ion transitions were m/z 316.2/298.0 and 316.2/241.0 for oxycodone, 302.2/284.0 and 302.2/227.0 for noroxycodone, 319.2/301.0 and 319.2/244.0 for oxycodone-d_3, and 305.2/287.0 and 305.2/230.0 for noroxycodone-d_3.

The standard curves ranged from 0.1 to 75 ng/ml and 1–22.5 ng/ml for oxycodone and noroxycodone (both from Cerrilliant Corporation Round Rock, TX, USA), respectively. The

curves were fitted with quadratic regression. Two QC plasma samples with either 0.6 ng/mL oxycodone and 3 ng/ml noroxycodone or 60 ng/ml oxycodone and 21.6 ng/ml noroxycodone were analysed each day of analysis, and relative standard deviation was ≤ 15% for oxycodone and ≤ 17% for noroxycodone.

Safety monitoring

Safety and tolerability evaluations included an assessment of adverse events. If necessary, monitoring of vital signs, oxygen saturation and physical examinations were performed. Subjects were asked before and 1.5, 3, 6, 12 and 24 h after drug administration to rate the degree of 10 well-known and/or common side-effects of oxycodone. The rating scale was as follows: (0) none, (1) slight, (2) moderate, (3) high degree and (4) very high degree. The sum of side-effects scores were compared between formulations by repeated measures ANOVA. $P < 0.05$ was considered significant and the statistical analysis was performed using R software [14] (Version 3.3.3).

General modelling procedure

Models were fitted to population data using non-linear mixed effect modelling (NONMEM) (version 7.4; ICON Development Solutions, Ellicott City, MD, USA) with the Wings for NONMEM interface (http://wfn.sourceforge.net) and IFort compiler. The first order conditional estimation with interaction (FOCE-I) analysis was used within NONMEM. Unless stated otherwise, the inter-individual variability of parameters was assigned a log-normal distribution across the population. A combined additive and proportional residual error model was used, but was reduced to either proportional or additive if an error term was very small and did not improve the model fit. Selection criteria for the base model were based on mechanistic plausibility, a statistically significant ($P < 0.05$) improvement of the fit (3.8-unit decrease in the objective function for the addition of a single parameter) and visual inspection of standard goodness-of-fit diagnostic plots. The final model was also required to pass the covariance step. Visual predictive checks (VPC) based on 1000 simulations of the index dataset were used to evaluate the predictive performance of the adequacy of the final model in describing the observed data.

A sequential PKPD modelling approach was used, whereby the PK component of the model was developed first, with the PD model developed sequentially using the PPP&D (Population PK Parameters and Data) method with the PK model parameters fixed at the previously determined values and the PK data retained during the PD model estimation step [15].

Models accounting for below limit of quantitation (BLOQ)-censored data were investigated using the YLO and M3 methods [16]. The YLO and M3 methods provide complimentary methods for attempting to utilize BLOQ data. With the YLO method likelihood assumes all values are censored at the lower limit of quantification. In contrast, the M3 method estimates the likelihood at times measurements BLOQ. We chose the M3 method (which does not assume that measurements are > 0) over the M4 method (which assumes measurement must be > 0). Although this may be controversial in the literature, we chose the M3 method as we believe that it is indeed theoretically possible that a measure concentration may be <0. Processing NONMEM output and generating plots were conducted with the R software [14] (Version 3.3.3 or later) using gglot2, plyr, doBy and scales packages and their associated dependencies.

Pharmacokinetic modelling

A PK model for oxycodone was developed and fitted simultaneously to the data from three formulations of oxycodone, thus allowing for differences in relative bioavailability (oral solution reference value 100%), absorption rate constants and absorption lag to be examined. Standard 1-, 2- and 3-compartment models with first-order absorption were fitted to the plasma oxycodone concentration-time data. Correlations between parameters were examined. The Omega BLOCK functionality of NONMEM was investigated on models that had highly correlated (>0.5) ETAs. All base models were investigated with allometric scaling with total body weight referenced to 70 kg and fixed exponents of 0.75 for clearance and 1 for volumes. Population parameters were tested for between-occasion variability as a random effect. Potential significant covariates were identified by visualising plots of covariates versus between-subject variability (BSV) of parameter estimates. Physiologically plausible covariates (e.g. vomit, sex, age) were evaluated for statistical significance using a stepwise covariate modelling of forward addition and backward elimination [17]. The statistical criteria for retaining a covariate in the model was $P < 0.01$ during forward addition and $P < 0.001$ for backward elimination.

Pharmacodynamic modelling

Direct effect, effect-compartment (linked effect) and turn-over models with linear, sigmoidal E_{max} and simple E_{max} concentration-relationships were tested as described in more detail by Upton et al., 2014 [18]. All models were tested with the oxycodone drug effect as either additive or proportional to the baseline value of the PD metric (pupil diameter). The distributions of the

baseline PD parameters were assumed to have a normal distribution. Potential covariates were screened and evaluated as described for the PK model development.

Simulations

Simulations, using the final PKPD model, were used to investigate the magnitude of a slower absorption rate constant for the controlled-release formulation (k_{aCR}) on specific pharmacokinetic and pharmacodynamics endpoints, thus predicting what might happen to the time-course of analgesia. The k_{aCR} could potentially be lower for patients with gastrointestinal dysfunctions such as Crohn's disease, due to a thickened bowel wall and mucosal lesions. Fat maldigestion, which also applies for patients with chronic pancreatitis, may also influence drug release for the lipid-based controlled-release formulation [19,20].

Simulations for 2000 subjects receiving 10 mg controlled-release oxycodone every 12 hours for 4 days were performed. Simulations were based on an individual weight set to 70 kg and performed for each sex. Two absorption rate constants were tested (125% and 150% of the final model absorption half-life). These values were chosen based on a previous modelling work on controlled-release oxycodone [21]. Non-compartmental exposure metrics of oxycodone concentrations (AUCt, C_{max} and T_{max}) and time to maximum PD effect (TPDMAX) and maximum PD effect (PD_{max}) were calculated based on the last dosing interval. Simulations were conducted using the mrgsolve package in the R software [14] (Version 3.3.3 or later).

Shiny application

The final model was incorporated within a Web application which allows users to rapidly simulate clinical scenarios. The application is built using the Shiny package for R, and simulations are performed using the mrgsolve package [22].

Statistical analysis

Previous bioequivalence studies have used 12-30 subjects. The present study used 3 cross-over arms, thus further increasing the power of the study. Thus, 15 subjects were considered an appropriate sample size. Demographic variables were compared using Student's t-test or Kruskal-Wallis Rank Sum Test, depending on data distribution, which was assessed using Shapiro Wilk testing and visual inspection of density plots and Q-Q plots. Statistical significance was assumed at $P < 0.05$. All data were analysed using the R software [14] (Version 3.3.3 or later).

Results

Study population and pharmacokinetic/pharmacodynamic data

Fifteen (8 males, 7 females) healthy opioid-naïve volunteers (mean age 32.2 ± 7.64, range 25-46 years) participated and completed all three treatment visits. Relevant demographics are summarised in Table 1. Benzoyl peroxide (N = 1) against acne and contraceptive methods (N = 6) were the only medications used amongst subjects. Significant sex differences were seen for height ($P = 0.001$) and weight ($P = 0.003$); however, there was no significant sex difference in body mass index ($P = 0.247$).

----------Table 1 near here ----------

In total, 850 blood samples were obtained and 853 pupil diameter measurements were performed. Overall, 7.4 % of the oxycodone plasma concentration data were unavailable. This was mainly due to plasma concentrations being below the lower level of quantification, predominately at the beginning or end of sampling periods. Additionally, 0.23 % of the pupil measurements were missing. This was due to one subject experiencing side-effects at the time of measurement and another subject not returning for the 24 h sampling. Measured data are presented in Figure 1. Models accounting for below the limit of quantitation (BLOQ)-censored data were investigated using the YLO and M3 methods [16]; however, these were characterised by unreliable minimisation and covariance step status. Samples below the limit of quantitation were thus excluded a priori from the data set (M1 method).

----------Figure 1 near here ----------

Pharmacokinetic model

The PK of the three oxycodone formulations was best described by a 2-compartment distribution model compared to 1-compartment or 3-compartment models (Table S1, supplementary information). The model was allometrically scaled for total body weight referenced to 70 kg. The model retained both a proportional and an additive residual error term. Structural covariates included a formulation effect on the first-order absorption rate which was 80.1% slower for the controlled-release tablets ($k_a = 0.94$ h^{-1} vs. 0.19 h^{-1} for the oral solution and controlled-release

formulations, respectively). Additionally, an absorption lag (ALAG) of 0.23 h was seen for the controlled-release tablets. The occurrence of vomiting, age and sex were tested as possible covariates, but no important relationships were found. A significant drop in the objective function was seen upon fitting separate absorption rate constants and bioavailability for the oral solution and controlled-release formulations. The estimated relative bioavailability and absorption rate constant were 0.33% and 1.1% different for the two controlled-release formulations compared to the oral solution, respectively. However, these models were largely over-parameterised (√condition number > 100) and/or did not pass the covariance step. Additionally, fitting a common bioavailability parameter for the two controlled-release did not improve the objective function. Therefore, both controlled-release formulations shared common parameters for the absorption rate-constant and the relative bioavailability was set to 1 for all formulations. Similarly, including between subject variability on bioavailability and absorption rate constant improved the model significantly, but this was discarded due to over-parameterisation of the model and an adverse impact on parameter precision. The final model population parameters are summarised in Table 2 and show good parameter precision (%SE < 30% for all parameters). The terminal half-life of oxycodone was estimated to be 3.2 h. Figure 2 presents the adequacy of the final model in key diagnostic plots following the three oxycodone formulations, with no major systematic bias in the structural and residual error models. The VPC plot of the final PK model showed good predictive performance for the observed oxycodone concentrations as represented by the good overlay of the median and 5^{th} percentiles and 95^{th} percentiles of the observed and the corresponding prediction intervals and 90% confidence intervals of the simulated concentrations (Figure 3). The model tends to slightly underpredict the observed 5th percentile of oxycodone concentrations; however, the observed median, 5^{th} and 95^{th} percentiles remain within the corresponding 90% confidence intervals of simulated concentrations (Figure 3). Similar VPC plots were obtained when oxycodone data were stratified on formulation (Figure S1, supplementary information).

----------Table 2 near here ----------

----------Figure 2 near here ----------

----------Figure 3 near here ----------

Pharmacodynamic model

Pupil diameter alteration was used as a PD endpoint for the CNS actions of oxycodone. Results from the modelling procedure indicated a proportional, E_{max} model linked to an effect-delay compartment to best explain the PD of oxycodone effect-delay. The delay between changes in plasma oxycodone concentration and effect was best described by an effect delay term (k_{e0}). In the final model, k_{e0} was estimated to be 2.92 h^{-1}, giving an effect delay half-life of about 14 min, with high inter-individual variability (BSV-SD = 0.516). A sex covariate was found on EC_{50} (concentration at which the effect is 50 % of E_{max} (maximum effect)), where the EC_{50} was 41.1 % lower for males (31.1 μg/L) compared to females (52.8 μg/L) indicating a higher potency of the total (bound + unbound) drug in males. The population estimates of the final PD model are summarised in Table 3 and show acceptable precision. Figure 4 shows the key diagnostic plots for the final PD model following the three oxycodone formulations. The individually predicted pupil diameters were comparable with the observed measurements with no indications of major bias. Model simulations were sufficient to describe the PD data for the different oxycodone formulations, as indicated by the VPC plots (Figure 5).

----------Table 3 near here ----------

----------Figure 4 near here ----------

----------Figure 5 near here ----------

Simulation

The population effects of a slower absorption rate constant are shown in Table 4. A 25% (k_{aCR} = 0.15) and 50% (k_{aCR} = 0.13) increase in absorption half-life resulted with an approximate 5% and 7% reduction of C_{max} for both sexes, respectively. These changes in absorption resulted in a maximum PD effect (PDmax) slightly decreased (as the pupil diameter 1 mm larger) for females. Time to PDmax was prolonged by 30 minutes for males.

----------Table 4 near here ----------

Shiny application

A "shiny" application for the final model can be assessed at (https://acp-unisa.shinyapps.io/oxycodonepkpd/). The application has been designed to allow users to assess the influence of covariates (formulation, sex and weight), varying dose-regimen and changes to the absorption rate constant on 1) the concentration-time profiles and exposure metrics of oxycodone, and 2) changes in pupil diameter, which is a surrogate for what might happen to the time-course of analgesia. Users may change parameter values and add prediction intervals by selection and/or changing the sliders. Users are required to click the "Simulation" button to update the plot after selecting the desired parameters' setting. Simulated exposure/response metrics data can be downloaded as a *.csv file by pressing the "download" button.

Safety assessments

No subject experienced any unknown, severe, harmful or persistent adverse event with regard to oxycodone. The most common side effects reported were sedation, dry mouth, dizziness and nausea. Four out of the fifteen subjects vomited at least once. A total of three subjects vomited after receiving the oral solution, two after the water-swellable controlled-release formulation and one after the lipid-based controlled-release formulation. All vomiting incidents occurred >2 h post-dose for the oral solution and >12 h post-dose for the controlled-release tablets. No difference in the overall degree of side-effects was reported for the three formulations ($P > 0.05$) (Figure 6).

----------Figure 6 near here ----------

Discussion

A population PKPD model was developed to describe the exposure-response relationship of oral solution and two monophasic controlled-release oxycodone formulations using data from 15 healthy subjects. The generically marketed controlled-release formulations had the same PD profile despite different formulation technologies, and there were no differences in the PK of these formulations. The controlled-release formulations differed from the oral solution by a delayed and

slower absorption, which explains the prolonged onset and offset of action. These findings are consistent with the marketed PK and PD properties of the applied study formulations. The model also indicated that oxycodone was more potent in males compared to females. Moreover, simulations revealed that the exposure-response relationship of controlled-release oxycodone was minimally affected for lower absorption rate constants.

Oxycodone pharmacokinetics

The PK of oral solution oxycodone in healthy subjects has previously been described by a one-compartment model with an absorption lag [23–26]. Results from work by Lalovic et al. also mainly supports a one-compartment model; however, they noted that some concentration-time profiles were better described by a two-compartment model [27]. Kokki et al. modelled the PK of several oxycodone formulations simultaneously (including intravenous, oral immediate-release and a biphasic oral controlled-release oxycodone) [28]. This model was based on data from elderly patients undergoing cystoscopy and showed that oxycodone pharmacokinetics was best described by a two-compartment model similar to that reported in the current paper. These findings highlight the limitation of an individual fitting iterative two-stage approach in comparison to the non-linear mixed-effects population approach used in the present work and by Kokki et al. (15). Additionally, parameter estimates were similar to those obtained by Kokki et al., but differed from the rest of the studies mentioned. Moreover, the terminal elimination half-life ($T_{½elim}$) of 3.2 h was within the range ($T_{½elim}$ = 2.3-6.7 h) of previously determined half-lives [26,28–33]. The controlled-release formulations showed a more gradual drug absorption compared to the oral solution. This was indicated by a lower absorption rate constant. Additionally, the bioavailability was best modelled as a fixed parameter set to 1, which implies that the relative bioavailability is 100%. Both findings are in agreement with results of Mandema et al. [26] and Kokki et al. [28]. In contrast to all above-mentioned studies, no lag time could be detected for the oral solution in this study. Possible reasons for these minor variations could be related to the limited number of subjects and large inter-individual variability in the PK profiles (Figure 1). This suggestion is partly supported by the observed over-parameterisation, when modelling separate lag times for the three formulations.

CNS effects

Lalovic and co-workers have described the concentration-analgesic relationship using pupillometry of oral immediate-release oxycodone by the classical E_{max} model with an effect delay

half-life ($t_{½}k_{eo}$) of 11 min [27]. This characterisation is in good accordance with our findings, although our model showed a slightly longer $t_{½}k_{eo}$ of 14 min. Other studies have described oral solution oxycodone by a linear effect relationship using subjective experimental pain measures and found no effect delay [24,25]. Staahl et al. found similar results, with effect delay ranging from 12-22 min for thermal and electrical skin stimulation [23].

Contradictory results regarding a correlation between opioid potency and gender exist [34–39]. In most animal studies, morphine and oxycodone had a higher potency in males compared to females [36,38]. Kim et al. found higher pain relief in men compared to females after equivalent oxycodone dosages [39]. In contrast, human males have been found to require 30-40% more morphine to obtain similar analgesic effects compared to females [34]. Similarly, a recent patient study also found that men required 28% more oxycodone than females to blunt the intubation reaction [37]. Our model found that oxycodone is more potent in males compared to females. Our finding suggests that the dose-effect difference between males and females is not due to pharmacokinetics, as no gender differences was found in the PK model. Nevertheless, it can be explained by an unknown sex-related pharmacodynamic mechanism for which we did not have a covariate to explain.

The PD effect of oxycodone was well described across formulations demonstrating different absorption profiles. We did not attempt to develop PK models for oxycodone metabolites. The main metabolite, noroxycodone, does not appear to exert central analgesic effects [27,40]. Oxymorphone, which is the second most abundant metabolite exhibits 8 times the potency and 40 times the affinity on μ-opioid receptor as compared to oxycodone. Despite this, the majority of studies suggest that the contribution of oxymorphone to the pharmacodynamic effects of oxycodone administrations is minimal, presumably attributed to the very low plasma concentrations, rapid glucuronidation to an inactive metabolite and/or the low rate of crossing the blood-brain-barrier [24,27,41–44]. Nevertheless, opposing results have been demonstrated by Samer et al., although the impact on pupil size was not as substantial as other pharmacodynamic parameters, thus questioning the central effects of oxymorphone [45]. Incorporating metabolites in future models could clarify this.

Simulations

The presented simulation results (Table 4) showed minimal alterations of PK and PD metrics for lower absorption rate constants. It is, however, important to emphasise that the performed

simulations lack essential physiological parameters. Thus, in reality, things may be very different and dosage adjustments may still be necessary for some patients to obtain satisfactory pain relief and prevent adverse events depending on the formulation design. More studies are needed to evaluate the clinical significance of these simulated results.

Degree of side-effects

In a study by Christrup et al., sedation tended to be more pronounced after an immediate-release formulation of morphine as compared to a controlled-release formulation [5]. Our results found no association between a higher degree of side-effects and formulation type. This result may be biased by the different dosages, where the oral solution was half that of the controlled-release formulations. Hence, fewer side-effects are likely reported for the oral solution.

Strengths and limitations

The randomisation and cross-over design, frequent, objective measurements and limited missing data strengthen the characterisation of the PKPD model by minimising bias, periodic effects and variance in PK and PD measurements. However, the design of this study also has some limitations. Subjective pain measurements would have supplemented the PD model, although these measurements often have drawbacks (e.g. limitation of frequent sampling, placebo-effect). Results from several studies have shown that pupillometry as used here is a valid biomarker for the central effects of opioids [8,11,46]. Additionally, a placebo treatment arm would have allowed for controlling for circadian modifications of the pupil diameter, which has been shown previously [47]. However, a placebo arm was not included due to practical and logistical issues. The duration of the study was 7 months, and including a placebo-arm would have expanded the study period significantly and participants would have had more days in the study. Additionally, the main aim of the study was to investigate pharmacokinetic differences between oral solution and two different controlled-release formulations. Thus, it was decided that the value of a placebo-arm was limited compared to the extra resources.

Subjects were discharged after 12 hours, as this was more convenient and less time-consuming for the subjects and study personnel. Nevertheless, we do not believe that this would introduce considerable variability to our data, because the measures are objective and oxycodone has a half-life of approximately 3 hours.

In contrast to the study by Kokki et al., the absolute bioavailability of the different formulations could not be estimated, as intravenous oxycodone data were not included in the design [28]. This was mainly due to the comprehensiveness of the study protocol. Additionally, more complex absorption models (slow and fast absorption) were not tested because the controlled-release formulations used in the current study were monophasic unlike the one used by Kokki et al. [28], which had a biphasic drug release.

While it might have been interesting to examine genetic polymorphisms of especially the μ-opioid receptor (OPRM1) and the metabolising enzymes CYP3A4/5 and CYP2D6, as potential covariates, the purpose of this work was focused on formulation effects on the PKPD profile of oxycodone. We can conclude that intestinal region-selective CYP450 expression does not impact the absorption processes of the different oxycodone formulations, as no differences in bioavailability was found between the oral solution and controlled-release formulations, despite clear differences in the time-course of absorption.

The establishment of the presented model is based on relatively young, healthy adults (age range 25-46 years), even though the included age range was deliberately broad to enhance the likelihood of matching future studies. Consequently, limiting predictions for other age groups, patients and different types of pain. However, the model can help outline possible differences in PKPD profiles, when comparing results obtained in patient groups with gastrointestinal dysfunction, when using the same medications and study design. Additionally, only monophasic preparations of two distinct controlled-release delivery systems were used. Results may therefore not be transferable to biphasic controlled-release formulations and other types of delivery systems.

In conclusion, a population PKPD model was developed for different oral oxycodone formulations based on data from healthy subjects. Expectedly, the diverse delivery systems of two monophasic controlled-release formulations had the same exposure-response relationship. Thus, indicating interchangeability in humans with normal gastrointestinal function. The controlled-release oxycodone formulations showed a smoother absorption profile and a prolonged onset and offset of action compared to oral solution oxycodone, thus being more suitable for persistent pain and chronic opioid users. The PD differences for the formulations were entirely explainable by pharmacokinetics differences secondary to different absorption profiles. Finally, the need for dosage adjustments to secure optimal oxycodone therapy for patients with gastrointestinal

dysfunction (e.g. Crohn's disease, chronic pancreatitis etc.) using different formulation designs, should still be investigated.

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References

1. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: The case for strategic prioritisation and action to improve knowledge and availability of appropriate care. BMC Public Health. 2013;13(1):1229.
2. Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Slavin K, Trescot AM, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician. 2017;20(2S):S3–92.
3. McCarberg BH. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. Am J Ther. 2001;8(3):181–6.
4. Rauck RL. What is the case for prescribing long-acting opiods over short acting opiods for patients with chronic pain - a critical review. Pain Pr. 2009;9(6):468–79.
5. Christrup LL, Sjøgren P, Jensen NH, Banning AM, Elbaek K, Ersbøll AK. Steady-state kinetics and dynamics of morphine in cancer patients: is sedation related to the absorption rate of morphine? J Pain Symptom Manage. 1999 Sep;18(3):164–73.
6. Martin C, De Baerdemaeker A, Poelaert J, Madder A, Hoogenboom R, Ballet S. Controlled-release of opioids for improved pain management. Mater Today. 2016;19(9):491–502.
7. Höfle M, Kenntner-Mabiala R, Pauli P, Alpers GW. You can see pain in the eye: pupillometry as an index of pain intensity under different luminance conditions. Int J Psychophysiol. 2008 Dec;70(3):171–5.
8. Fischer IW, Hansen TM, Lelic D, Brokjær A, Frøkjær JB, Christrup LL, et al. Objective methods for the assessment of the spinal and supraspinal effects of opioids. Scand J Pain. 2017;14:15–24.
9. Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny GN. Effect site concentrations of remifentanil and pupil response to noxious stimulation. Br J Anaesth. 2003;91(3):347–52.
10. Connelly MA, Brown JT, Kearns GL, Anderson RA, St Peter SD, Neville KA. Pupillometry: a non-invasive technique for pain assessment in paediatric patients. Arch Dis Child. 2014;99(12):1125–31.
11. Brokjær A, Olesen AE, Kreilgaard M, Graversen C, Gram M, Christrup LL, et al. Objective markers of the analgesic response to morphine in experimental pain research. J Pharmacol

Toxicol Methods. 2015;73:7–14.
12. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies. Basic Clin Pharmacol Toxicol. 2018;123(3):233–5.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
14. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [Internet]. 2014 [cited 2018 Dec 20].Available from: http://www.r-project.org/
15. Zhang L, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. J Pharmacokinet Pharmacodyn. 2003 Dec;30(6):387–404.
16. Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001 Oct;28(5):481–504.
17. Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic--pharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm. 1992 Oct;20(5):511–28.
18. Upton RN, Mould DR. Basic concepts in population modeling, simulation, and model-based drug development: Part 3-introduction to pharmacodynamic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2014;3(1):1–16.
19. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017 Apr 29;389(10080):1741–55.
20. Dressman J, Lennernäs H. Oral drug absorption prediction and assessment. 1st ed. Marcel Dekker, Inc.; 2000. 25–30 p.
21. Kim J-Y, Lee S-H, Park C-W, Rhee Y-S, Kim D-W, Park J, et al. Design and in vivo evaluation of oxycodone once-a-day controlled-release tablets. Drug Des Devel Ther [Internet]. 2015 [cited 2017 Feb 23];9:695–706.Available from: http://www.ncbi.nlm.nih.gov/pubmed/25678774
22. R studio, Inc. 2015. Shiny: web application framework for R. R package version 1.3.2. R Project for Statistical Computing, Vienna, Austria. Available from: https://cran.r-project.org/package=shiny
23. Staahl C, Upton R, Foster DJR, Christrup LL, Kristensen K, Hansen SH, et al.

Pharmacokinetic-pharmacodynamic modeling of morphine and oxycodone concentrations and analgesic effect in a multimodal experimental pain model. J Clin Pharmacol. 2008;48(5):619–31.

24. Olesen A, Upton R, Foster D, Staahl C, Christrup L, Arendt-Nielsen L, et al. A pharmacokinetic and pharmacodynamic study of oral oxycodone in a human experimental pain model of hyperalgesia. Clin Pharmacokinet. 2010;49(12):817–27.
25. Olsen R, Foster DJR, Upton RN, Olesen AE, Ross JR, Droney J, et al. Modelling the PKPD of oxycodone in experimental pain — impact of opioid receptor polymorphisms. Eur J Pharm Sci. 2016;86:41–9.
26. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol. 1996;42(6):747–56.
27. Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen LY, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther. 2006;79(5):461–79.
28. Kokki M, Välitalo P, Rasanen I, Sirpa Aaltomaa, Ojanperä I, Matti Eskelinen, et al. Absorption of different oral dosage forms of oxycodone in the elderly: a cross-over clinical trial in patients undergoing cystoscopy. Eur J Clin Pharmacol. 2012;68(10):1357–63.
29. Liukas A, Kuusniemi K, Aantaa R, Virolainen P, Neuvonen M, Neuvonen PJ, et al. Plasma concentrations of oral oxycodone are greatly increased in the elderly. Clin Pharmacol Ther. 2008;84(4):462–7.
30. Leow KP, Smith MT, Watt JA, Williams BE, Cramond T. Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration. Ther Drug Monit. 1992 Dec;14(6):479–84.
31. Poyhia R, Seppala T, Olkkola K, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. Br J Clin Pharmacol. 1992;33(6):617–21.
32. Leow KP, Smith MT, Williams B, Cramond T. Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. Clin Pharmacol Ther. 1992 Nov;52(5):487–95.
33. Benziger DP, Miotto J, Grandy RP, Thomas GB, Swanton RE, Fitzmartin RD. A pharmacokinetic / pharmacodynamic study of controlled-release oxycodone. J Pain

Symptom Manag. 1997;13(2):75–82.
34. Pleym H, Spigset O, Kharasch ED, Dale O. Gender differences in drug effects: Implications for anesthesiologists. Acta Anaesthesiol Scand. 2003;47(3):241–59.
35. Sarton E, Olofsen E, Romberg RR, den Hartigh J, Kest B, Nieuwenhuijs D, et al. Sex differences in morphine analgesia. Anesthesiology. 2000;93(5):1245–54.
36. Dahan A, Kest B, Waxman AR, Sarton E. Sex-specific responses to opiates: animal and human studies. Anesth Analg. 2008 Jul;107(1):83–95.
37. Kang X-H, Bao F-P, Zhang H-G, Yu D-J, Ha K, Xie Q, et al. Gender affects the median effective dose and 95% effective dose of oxycodone for blunting the hemodynamic response to tracheal intubation in narcotic-naïve adult patients. Chin Med J (Engl). 2018;131(16):1958.
38. Collins D, Reed B, Zhang Y, Kreek MJ. Sex differences in responsiveness to the prescription opioid oxycodone in mice. Pharmacol Biochem Behav. 2016 Sep;148:99–105.
39. Kim S-I, Ha K-Y, An HS, Rhyu K-W, Lee H-W, Oh I-S. Sex-specific and age-specific analgesia for early postoperative pain management after lumbar decompressive surgery. Clin Spine Surg. 2018 Dec;1.
40. Nieminen TH, Hagelberg NM, Saari TI, Pertovaara A, Neuvonen M, Laine K, et al. Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009 Jun;110(6):1371–8.
41. Mikus G, Klimas R. Contribution of oxycodone and its metabolites to the analgesic effect. Br J Anaesth. 2014 May;112(5):944–5.
42. Klimas R, Witticke D, El Fallah S, Mikus G. Contribution of oxycodone and its metabolites to the overall analgesic effect after oxycodone administration. Expert Opin Drug Metab Toxicol. 2013;9(5):517–28.
43. Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. Clin Pharmacol Ther. 1996 Jan;59(1):52–61.
44. Smith DM, Weitzel KW, Elsey AR, Langaee T, Gong Y, Wake DT, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genet Med. 2019 Jan 23;
45. Samer C, Daali Y, Wagner M, Hopfgartner G, Eap C, Rebsamen M, et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a

major effect on oxycodone analgesic efficacy and safety. Br J Pharmacol. 2010;160(4):919–30.

46. Stoops WW, Glaser PEA, Rush CR. Miotic and subject-rated effects of therapeutic doses of tapentadol, tramadol, and hydromorphone in occasional opioid users. Psychopharmacology (Berl). 2013;228(2):255–62.

47. Van Egroo M, Gaggioni G, Cespedes-Ortiz C, Ly JQM, Vandewalle G. Steady-State Pupil Size Varies with Circadian Phase and Sleep Homeostasis in Healthy Young Men. Clocks & Sleep. 2019;1(2):240–58.

Tables

Table 1. Study population characteristics.

	Female	Male	*P*-value
No. of subjects	7	8	-
Age (yrs.)	35.00 (9.24)	29.75 (5.39)	0.195
Height (cm)	170.86 (6.47)	186.38 (7.35)	0.001
Weight (kg)	68.63 (8.84)	86.39 (10.18)	0.003
BMI (kg/m^2)	22.30 [21.70 - 25.61]	24.03 [23.13- 26.03]	0.247

Data are expressed as mean (standard deviation) or median [interquartile range]. Group comparisons were performed using Student's *t*-test or the Kruskal-Wallis Rank Sum Test, depending on data distribution. BMI = body mass index.

Table 2. Pharmacokinetic parameter estimates for the best pharmacokinetic model.

Parameter	Symbol	Unit	Pop value[a]	%RSE	BSV(SD)	%RSE	ETA *P* value	Shrinkage (%)
CL/F	Θ_1	L/h	79.4	9.0	0.318	11.8	0.992	0
V_1/F	Θ_2	L	80.1	29.3	1.005	17.3	0.985	0.7
Q/F	Θ_3	L/h	83.3	24.0	-	-	-	-
V_2/F	Θ_4	L	164	7.0	-	-	-	-
k_{aSOL}	Θ_5	h^{-1}	0.94	26.0	0.342	16.8	0.984	5.9

k_{aCR}	Θ_6	ratio	-0.801	4.4	-	-	-	-
ALAG	Θ_7	h	0.23	2.9	-	-	-	-
Residual error								
Proportional error (ERRCV)	σ_1	%CV	37.4	7.1	-	-	-	-
Additive error (ERRADD)	σ_2	µg/L	0.5	19.3	-	-	-	-

CL = total body clearance; F = bioavailability; V_1 (or V_2) = volume of first (or second) compartment; Q = inter-compartmental clearance; k_{aSOL} = absorption rate constant for the oral solution; k_{aCR} = effect on absorption rate constant for the controlled-release formulations; ALAG = lag time for the controlled-release formulations %RSE = percent of relative standard error; BSV = between subject variability; SD = standard deviation; %CV = percent coefficient of variation. Symbols relate to the control stream (Please see the supplementary information); Θ = THETA, σ = SIGMA.

[a]Population typical value. Bioavailability was best modelled as a fixed parameter = 100 %.

Table 3. Pharmacodynamic parameter estimates for the best pharmacodynamic model.

Parameter	Symbol	Unit	Pop value[a]	%RSE	BSV(SD)	%RSE	ETA *P* value	Shrinkage (%)
E_{BASE}	Θ_8	mm	5.4	2.4	0.169	13.7	0.955	0
EC_{50}	Θ_9	µg/L	52.8	15	0.227	15.5	0.823	8.1
ke_0	Θ_{10}	h^{-1}	2.92	3.1	0.516	72.2	0.843	17.1
SEXCOV	Θ_{11}	ratio	-0.411	32.8	-	-	-	-
Objective function			2671.56					
Residual error								
Proportional error (ERRCVPD)	σ_3	%CV	9.2	5.6	-	-	-	-

E_{BASE} = baseline effect; EC_{50} = concentration at which the effect is 50 % of E_{max} (maximum effect); ke_0 = effect compartment elimination rate constant; SEXCOV = effect of male sex on EC_{50}; %RSE = percent of relative standard error; BSV = between subject variability; SD = standard deviation; %CV = percent coefficient of variation. Symbols relate to the control stream (Please see the supplementary information); Θ = THETA, σ = SIGMA.

Table 4. Simulation results and predicted effects on pharmacokinetic and pharmacodynamic endpoints for 10 mg controlled-release oxycodone, stratified by sex.

Formulation	Metric	Female			Male		
		PKPD model (k_{aCR} = 0.19)	k_{aCR} = 0.15	k_{aCR} = 0.13	PKPD model (k_{aCR} = 0.19)	k_{aCR} = 0.15	k_{aCR} = 0.13
10 mg controlled-release oxycodone	AUC_t (ng·h/ml)	126.5	126.5	126.5	126.5	126.5	126.5
	C_{max} (ng/ml)	21.9	20.8	20.4	21.9	20.8	20.4
	T_{max} (h)	2.5	2.5	2.5	2.5	2.5	2.5
	PD_{max} (mm)	3.6	3.7	3.7	3.2	3.2	3.2
	TPD_{max} (h)	3.5	3.5	3.5	3.0	3.5	3.5

k_{aCR} = absorption rate constant for the controlled-release tablets; AUC_t = area under the concentration curve, C_{max} = maximum concentration; T_{max} = time to maximum concentration; PD_{max} = minimum pupil size (maximum effect); TPD_{max} = time to maximum effect (PD_{max}). All metrics are based on the last dosing interval.

Figure legends

Figure. 1. Observed oxycodone plasma concentrations and pupil diameter data by formulation.
Oxycodone plasma concentration is shown in red. Pupil diameter is shown in blue. Symbols are measured data. Solid line is the median of the measured data. Data are log-transformed. CRF = controlled-release formulation.

Figure 2. Diagnostic plots for oxycodone concentrations following oral solution oxycodone (red), controlled-release water-swellable oxycodone tablets (blue) and controlled-release lipid-based oxycodone tablets (green).
Symbols are data points, the solid black line is a line of identity with slope 1 or 0, and the red lines are a loess-smooth of the data. CWRES = conditional weighted residuals, conc = concentration, CRF = controlled-release formulation.

Figure 3. Visual predictive check of oxycodone using the final pharmacokinetic model.
Symbols represent observed oxycodone concentrations. The shaded areas represent the 90% confidence interval of the 5^{th}, 50^{th}, 95^{th} percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations. The dashed red lines represent the 5^{th} and 95^{th} percentiles of the observed concentrations. The horizontal dotted lines represent the lower limit of quantitation of oxycodone. The black lines represent the predicted median with the 5^{th} and 95^{th} percentiles.

Figure 4. Diagnostic plots for pupil diameter following oral solution oxycodone (red), controlled-release water-swellable oxycodone tablets (blue) and controlled-release lipid-based oxycodone tablets (green).
Symbols are data points, the solid black line is a line of identity with slope 1 or 0, and the red lines are a loess-smooth of the data. CWRES = conditional weighted residuals, CRF = controlled-release formulation.

Figure 5. Visual predictive checks of the different oxycodone formulations using the pharmacodynamic model.
Symbols represent observed pupil diameter. The shaded areas represent the 90% confidence interval of the 5^{th}, 50^{th}, 95^{th} percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations. The dashed red lines represent the 5^{th} and 95^{th} percentiles of the observed concentrations. The black lines represent the predicted median with the 5^{th} and 95^{th} percentiles. CRF = controlled-release formulation.

Figure 6. Total rating of side effects over time for each oxycodone formulation. No overall difference in total side effect scores was found between any of the formulations ($P > 0.05$). Vertical lines represent the standard error of the mean. Dots represent individual side effect scores. CRF = controlled release formulation, h = hours.

Figures

Figure 1.

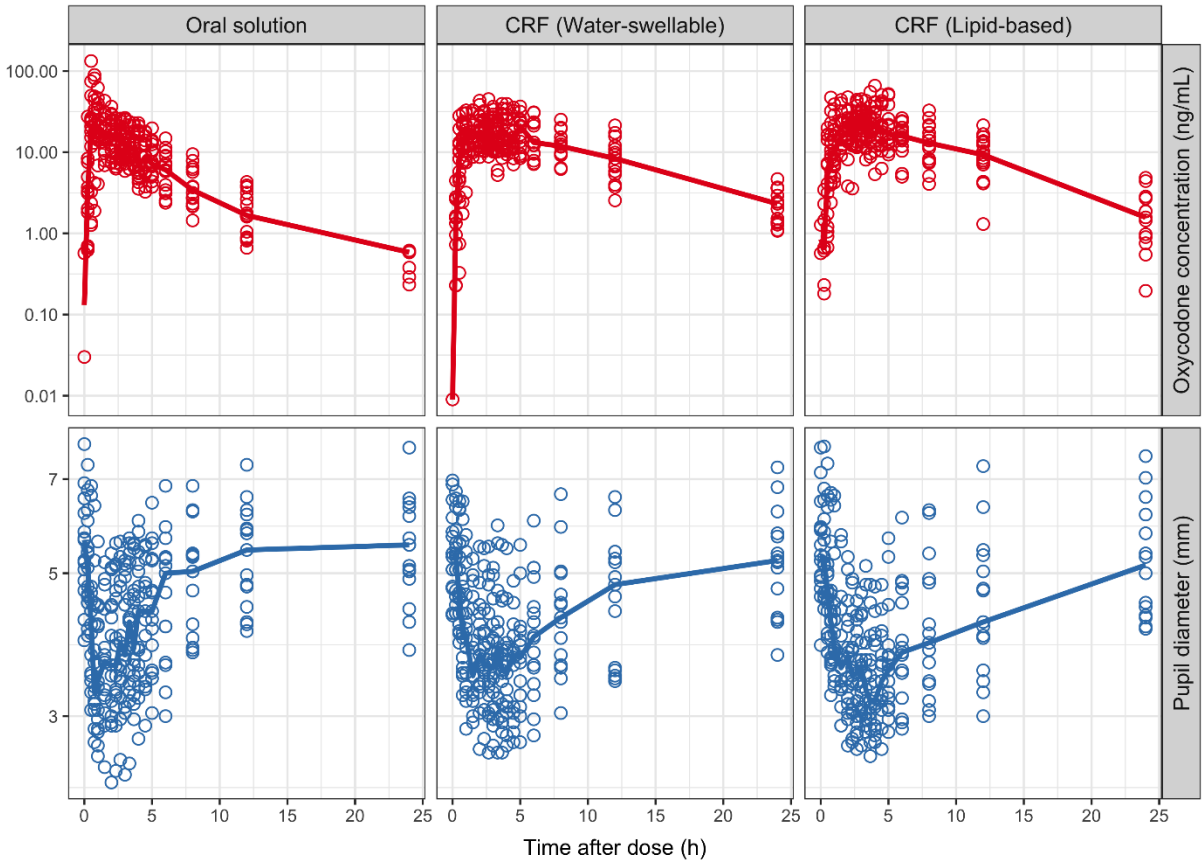
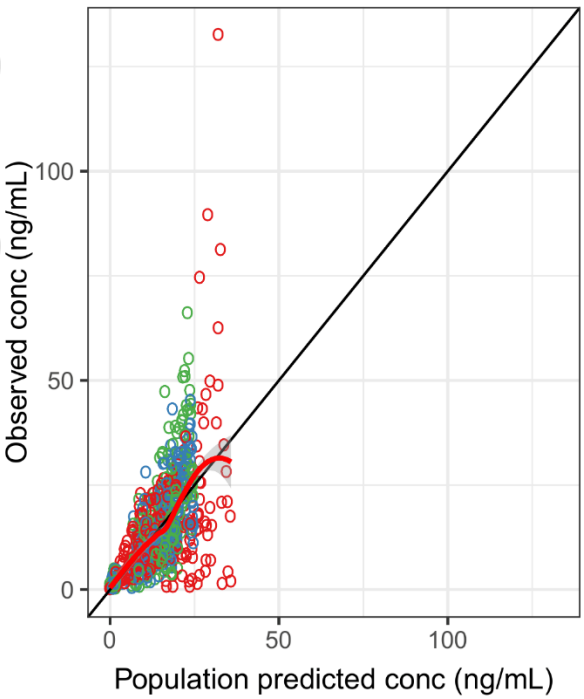
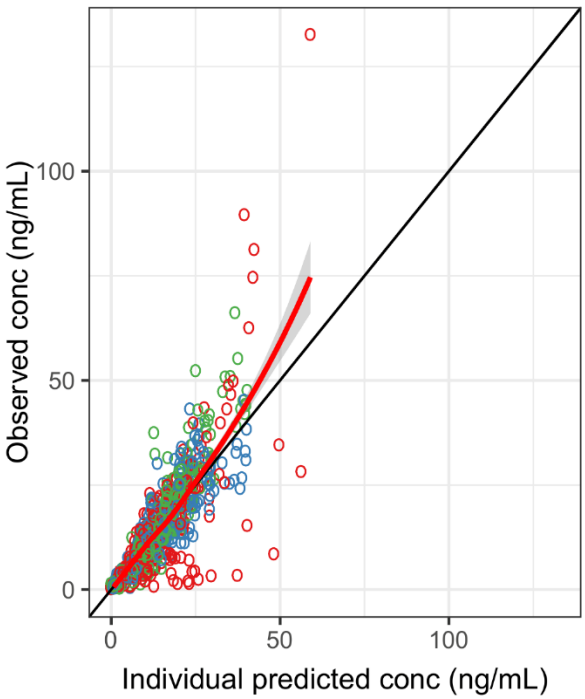
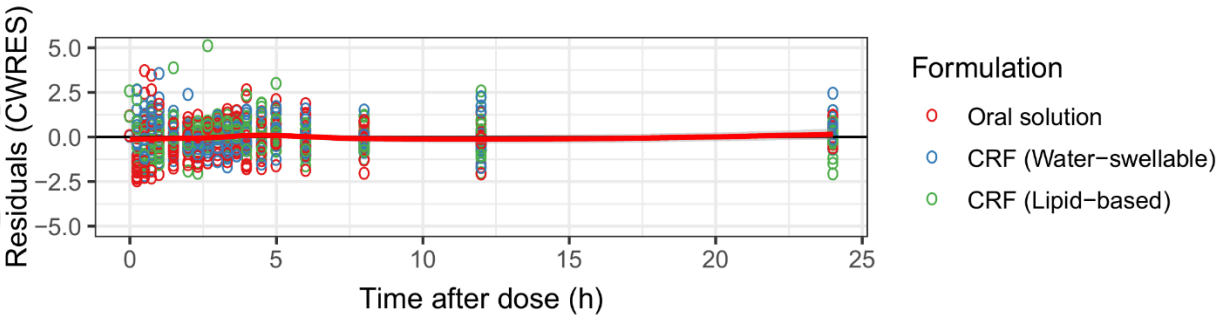


Figure 2.







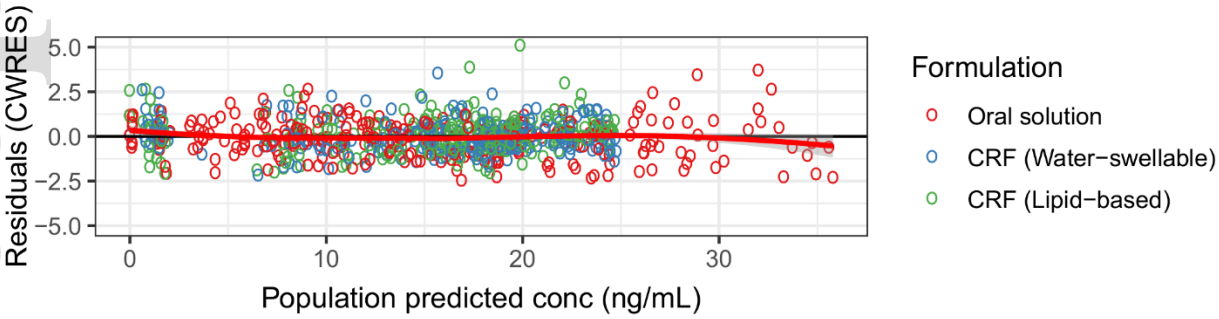


Figure 3.

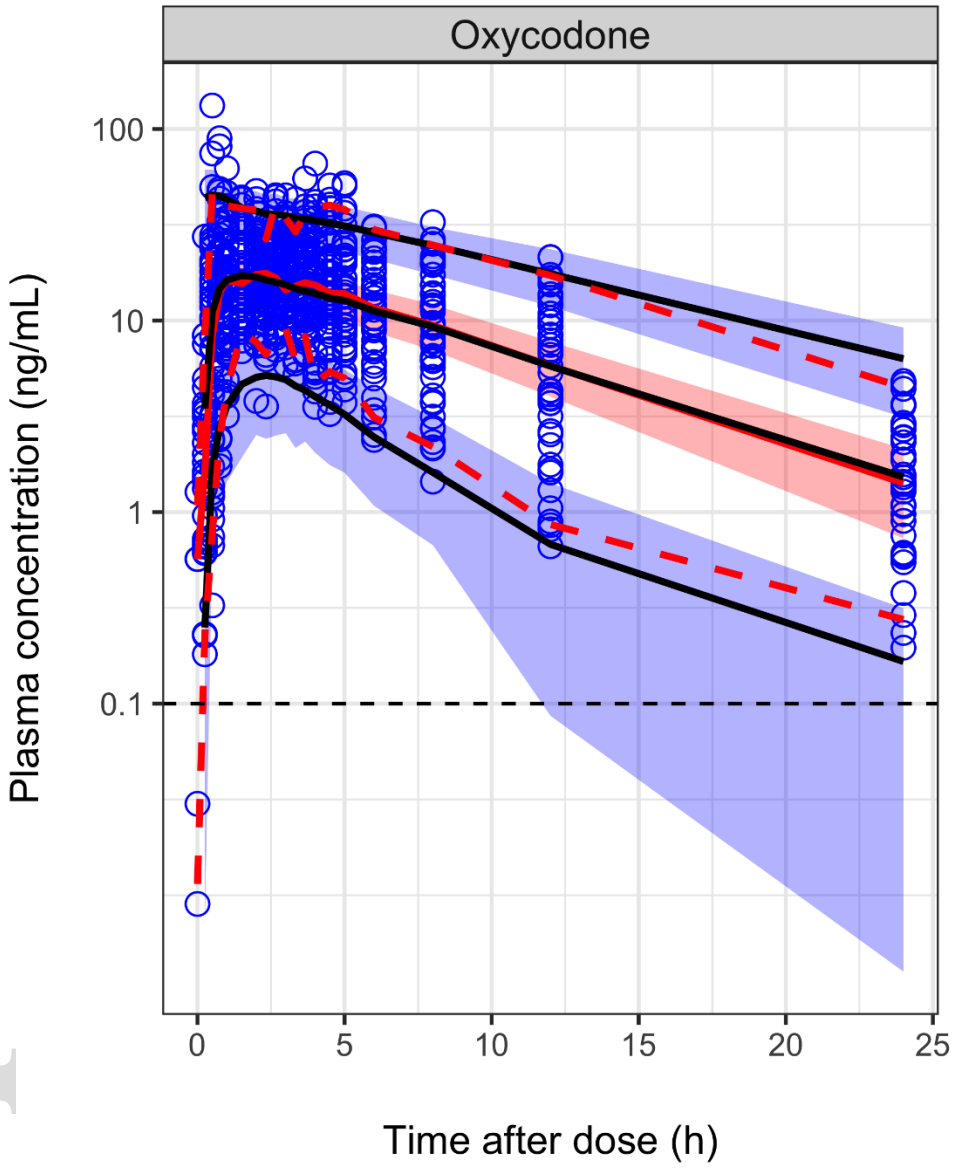


Figure 4.

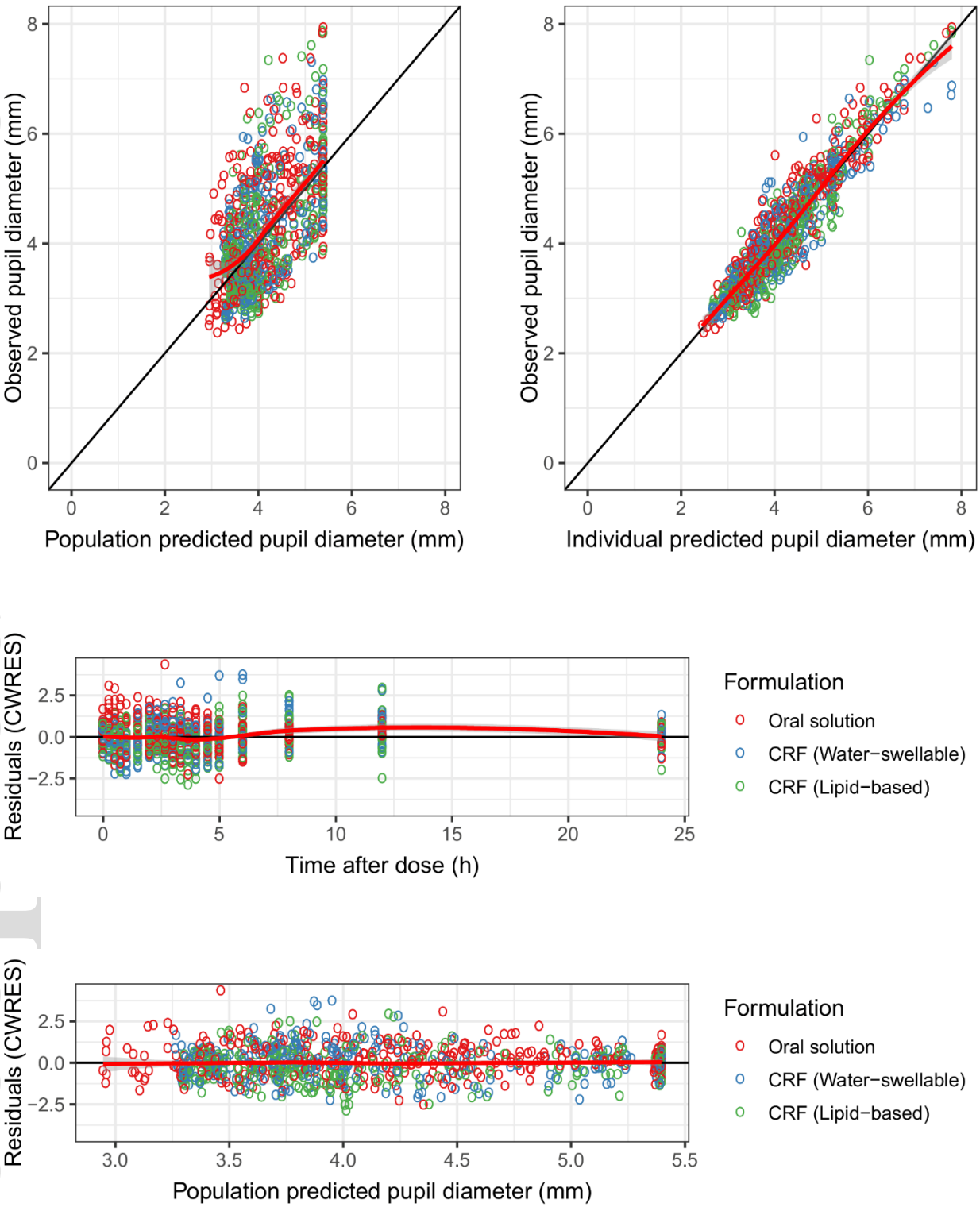


Figure 5.

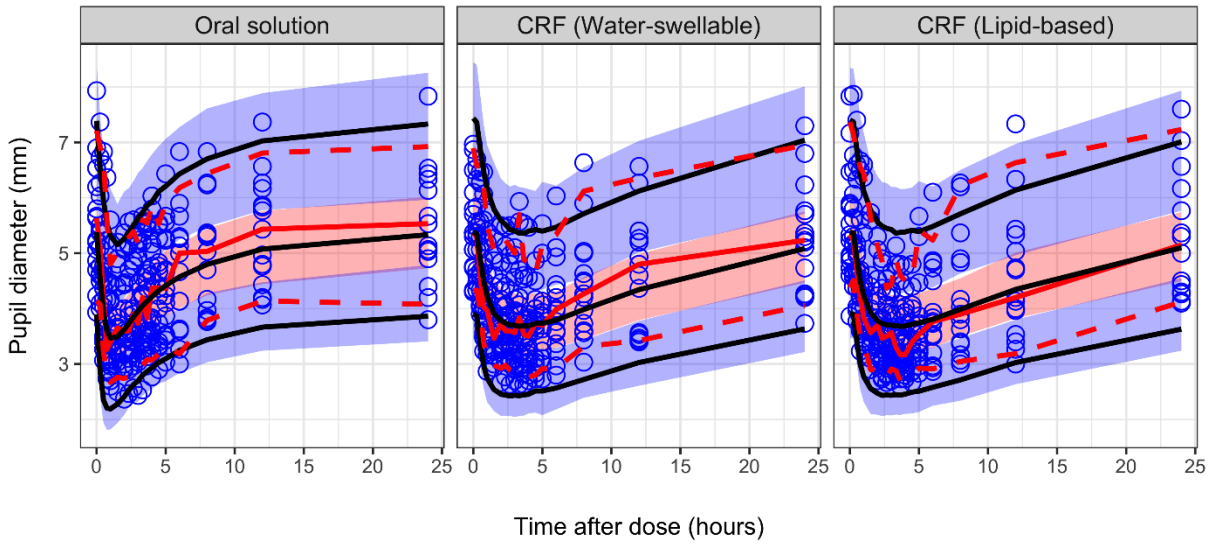


Figure 6.